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Biocompatibility and effectiveness of a novel organic olive oil-based denture adhesive: A multicenter randomized and placebo-controlled clinical trial

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Abstract: To assess the clinical efficacy of a novel organic olive oil-based denture adhesive and its effect on *Candida Albicans* growth in maxillary edentulous individuals wearing complete dentures. Individuals were selected from two Dental Schools in Portugal and Spain. Twenty-eight complete dentures were relined, following a standardized protocol. The novel product (Test) was compared with a commercialized adhesive (Control) and Vaseline (Placebo) randomly assigned in a cross-study design. The retention resistance was measured with a Gnathometer and a dynamometer, the patient related outcome evaluations with a 5-points questionnaire and the *Candida albicans* growth in a Sabouraud dextrose agar (SDA) medium in order to evaluate differences between the placebo and experimental product. Twenty-three participants were included. Dynamometer evaluation showed significant differences between not using a denture adhesive and using either (experimental, $p = .03$; control, $p = .04$), no significant differences between the two adhesives ($p > .05$). In the subjective analysis, the experimental adhesive showed a significantly longer effectiveness ($p = .001$); the control reported better results at taste ($p = .03$) in chewing ($p = .001$). The test adhesive showed better ($p < .001$) *Candida albicans* growth inhibition. The experimental adhesive showed longer effectiveness than the control and placebo with a better inhibition capacity for the growth of *Candida albicans*, patients reported better abilities for speech, chewing, taste and retirement in the control adhesive.

Keywords: Prosthodontics; Edentulism; Elderly; Complete Denture; *Candida Albicans*, Antimicrobial activity

1. Introduction

Complete dentures continue to be a reliable treatment option for edentulous patients due to medical and economic constraints. [1] Denture's retention, stability, and support depend on the intimate adaptation of its base to the soft and hard tissues, the peripheral

seal fir, and the presence of saliva between the denture and the intraoral tissues. [2,3] However, in several clinical situations, the natural adhesiveness of saliva, the denture base design and extension cannot provide enough stability and retention. In those cases, denture adhesives proved to be a good option for patients by increasing comfort levels and ultimately improving performance in function. [4,5]

Effective action mechanisms of denture adhesives depend on the combination of physical and chemical forces. [6] When in contact with saliva, denture adhesives increase by 50% to 150% in volume, mainly due to the hydrophilic nature of some of their components. Thus, they eliminate the empty spaces between the underlying oral mucosa and the denture's base, and ultimately improve the peripheral sealing and increase denture's stabilization and retention. [6]

In the last decades, several studies have been published to determine the effectiveness of denture adhesives. [2,7] Regardless of the various methods used, most of the studies concluded that denture adhesives improve stability and retention and, therefore, contribute to greater user satisfaction and confidence. [7,8,9,10,11,12,13,14,15]

Besides retention, another clinical issue that denture wearers often face is oral tissue infection. *Candida albicans* is a commensal in the oral cavity of 45–65% of healthy individuals. [16,17] In denture wearers, the prevalence of *Candida* increases from 60 to 100%. [16,18] Several studies have investigated the effect of denture adhesives on the oral microbiota but with contradictory results. One study [19] showed that *Candida Albicans* growth in vitro was potentiated by some denture adhesives, while in other [20], denture adhesives showed antifungal behavior. [19,20]

Therefore, the aim of this clinical study was to assess the efficacy of a novel organic olive oil-based denture adhesive in maxillary edentulous patients wearing complete dentures. Patient-centered outcomes associated with denture adhesives use, such as perceived degree of retention, patient satisfaction, and time of effectiveness were evaluated, as well as the growth of *Candida Albicans* in vitro in the presence of both denture adhesives. The null hypothesis was that there were no statistically significant differences between the novel adhesive (test), the conventional adhesive (control) and the placebo adhesive for the clinical outcomes (retention, patient satisfaction, time of effectiveness) and in the *Candida Albicans* growth.

2. Materials and Methods

2.1. Study design

A randomized controlled clinical trial was designed following CONSORT guidelines [15] and performed at the Department of Prosthodontics of the Faculty of Dentistry of the Complutense University of Madrid and at the Oral Rehabilitation Unit of the Faculty of Dental Medicine of the Portuguese Catholic University. The protocol was evaluated and approved by the Research Ethics Committee of the Clínico San Carlos Hospital of Madrid, Spain (Trial registration code CEIC 18/515-R_P) following the Declaration of Helsinki of ethical principles for medical research involving human subjects. Informed consent was obtained from all participants prior to conducting the research.

2.1. Study participants

The sample size was calculated based on the expected effect for the control adhesive, [10] using an alpha value of .05 and a statistical power of 80% (G-Power v. 3.1.9.2, Germany). Patients were selected from a convenience sample at the Department of Prosthodontics of the Faculty of Dentistry of the Complutense University of Madrid and at the Oral Rehabilitation Unit of the Faculty of Dental Medicine of the Portuguese Catholic University.

Inclusion criteria were as follows: participants older than 18 years, fully edentulous for at least one-year, maxillary dentures fabricated within the previous 2 years, availability for the study appointments, and with confirmed absence of allergic sensitivity to the denture adhesive components. Patients with poor oral hygiene or incapable of doing it

correctly, incapable of clear communication due to neurologic diseases, or with temporomandibular disorders were excluded from this study.

2.3. Study intervention

The dentures were clinically relined with a hard-reline resin material (Ufi Gel hard C, VOCO, Germany) according to the manufacturer's protocol. The same type of teeth was used for all dentures (SR Orthotyp PE for posterior teeth and SR Vivadent PE for anterior teeth, Ivoclar Vivadent, Lichtenstein) to ensure similar contact/wear. A bilateral balanced occlusal scheme was ensured and verified in all participants. (...) Once relined, dentures were evaluated for accuracy and correct adjustment. Participants were asked to wear them for two weeks, to allow dentures to adjust and achieve a good fit. After this period, if no mucosa lesion was found, participants entered the experimental part of the study.

2.4. Experimental design

An international multicenter crossover, randomized, triple-blinded clinical trial with a 2-week clearance period was adopted. After a 2-week adaptation period with the relined dentures, participants had a baseline-recording visit. During this appointment, initial retention values were registered using a gnathometer and a dynamometer. The initial participant-centered outcomes were also recorded in a questionnaire.

Participants were randomly assigned through Microsoft Excel 2010 software (Microsoft Co, Redmond, WA, USA) for the one of the test products. Participants were instructed on how to use the test products (amount, application, and cleaning process) and were asked to use them in the following two weeks.

At the 2-week evaluation visit, the same outcomes measurements were registered, and participants completed another questionnaire. After this visit, participants were instructed to continue using their dentures for the following two weeks but without using any product (clearance period). After this period, participants were again asked to use a newly assigned product for another two weeks, and similar baseline and 2-week evaluations were made. Once each participant had completed the study using the three products, the visits scheme was repeated.

2.4. Study materials

- Control adhesive (A): Conventional denture adhesive, (Kukident Pro®, Procter and Gamble, USA) cream form, composed of PVM/MA copolymers, liquid paraffin, sodium celluloses, petrol, colorings, preservatives, and aromatic particles.
- Experimental denture adhesive (B): Novel adhesive, (OlivaFix® Gold, Bonyf AG, Lichtenstein) cream formulated with 30% extra virgin organic olive oil, with no zinc or mineral oil or Vaseline.
- Placebo adhesive (C): Vaseline (Vaseline, Senti2®, Spain).

The three tested adhesives were blinded and transferred into identical containers labeled A, B, and C, for the further assessment. For the clinical evaluation of the dentures' stability and retention, a disposable gnathometer (Procter and Gamble Co., Cincinnati, OH, USA) and a dynamometer (Correx, Haag-Streit, Bern, Switzerland) were used.

A gnathometer measures the occlusal force necessary to dislodge a complete denture when the two arches occlude simultaneously. The participant bites until the denture moves and the indicator records it on a decimal scale, from 0 to 10 units (gnathometer units). When the result of the measurement was between two units, the lowest was registered. The measurements were repeated three times, with a one-minute interval, in three locations: the incisors and between the left and right first molars. The mean value of these measurements was used for the analysis.

A dynamometer measures quantitatively [grams (g)] the force necessary to dislodge the denture from the residual ridge of the patient when traction is applied. Three records

were made firstly in the anterior area of the frenulum and then in the posterior lateral areas. The mean value of these measurements was used for the analysis.

2.5. Outcome variables

The main assessed variables were the dentures' retention and stability, measured using the gnathometer and the dynamometer, as previously described. The participant-centered outcomes were recorded using a questionnaire. This questionnaire evaluated, on a scale of five items (very good, good, moderate, minimal or very bad), the participant's subjective evaluation of the following variables: retention and stability, taste and consistency of the denture adhesive, denture adhesive intra-orally removal capacity and the participant's willing to use the denture adhesive again. The clinical protocol and the questionnaire were adapted from Pradíes et al. [10]

2.6. Pilot study – inter- and intra-observer reliability

A pilot clinical study was performed to determine the intra-observer measurement variability. In each Faculty, five participants with complete maxillary dentures were selected. Participants had a natural dentition, a fixed prosthesis, or a removable prosthesis (on teeth or implants) in the antagonist arch. For each participant, the primary evaluator made six measurements (three with the dynamometer and three with the gnathometer only in the anterior area) with a one-minute break. One week later, in the same period of the day, the measurements were repeated for each participant with the same gnathometer. The measurement deviation was calculated using the Dahlberg formula, and the Pearson correlation was calculated as the reliability coefficient.

Another pilot study was carried out in the clinic of the Faculty of Dental Medicine of the Portuguese Catholic University, Portugal, to determine the interobserver concordance. Two main evaluators used the same gnathometer and dynamometer to obtain the corresponding measurements in all participants. They made three measurements in the anterior area, and the average value was used in the analysis. All measurements were made after a one-minute break to allow the participant to restore the denture comfortably. A three-way analysis of variance (ANOVA) was applied to evaluate the influence of the observers, because of the possible learning effect, while correcting for patient influences. The measurement error was calculated by the Dahlberg formula, and the concordance coefficient was calculated by the Pearson correlation.

2.7. Effect of denture adhesives on *Candida Albicans* growth

The in vitro evaluation of the effect of denture adhesives on the growth of *Candida Albicans* ATCC 11225 was evaluated in solid (Sabouraud dextrose Media), following protocols similar to those used by Sampaio-Maia et al. [17] Saturated solutions of the denture adhesives (1% w/v) were prepared in sterile saline solution (NaCl 0.9%) and added to a sterile Sabouraud dextrose agar (SDA), thereafter each plate (20ml) of SDA received 1ml of denture adhesive solution and were inoculated in triplicate with 0.5ml of a standardized inoculum of 1×10^6 cells/ml of *C. albicans* ATCC11225 and incubated at 25°C for a week. The plates were observed at 48 hours, 72 hours, and one week, and the colony forming units (CFUs) were counted.

2.8. Stistically data analysis

Collected data was transferred to a database (Microsoft Excel, Microsoft, USA), and analyzed by two independent researchers. Subsequently, data were statistically processed with SPSS (SPSS for Windows, version 25, SPSS Inc., Chicago IL, USA). For each test, normality was verified with Kolmogorov-Smirnov and Shapiro-Wilk statistical tests. For the quantitative questions, the Kruskal-Wallis test was used to analyze possible differences between the test products in the absence of normality. In the presence of differences, the Mann-Whitney test was applied to the results of each product separately and the Bonferroni correction to combination of two. When normality was verified, an ANOVA was

used, as well as the post-hoc Bonferroni test. The qualitative questions were expressed in percentages and with a chi-square test.

Results of the in vitro analysis were expressed in CFU/milliliter, corresponding to cells/milliliter. All measurements were obtained in triplicate, and all tests were repeated once. Means were calculated, and the results were compared with a Student's t-test or with an ANOVA analysis. For all tests, $\alpha = .05$ was used, and p -values equal to or less than .05 ($p \leq .05$) were considered statistically significant.

3. Results

3.1. In vivo assessment

Thirty-two patients were recruited to participate in this study and finally 28 participants were included: 12 (42.86%) in the Complutense University of Madrid and 16 (57.14%) in the Portuguese Catholic University. Five (17.86%) individuals did not complete the experimental part of the study and were not considered in the evaluation. The remaining participants ($n = 23$) completed the study. Most of the participants were older than 65 years (y) old ($n = 15$; 65.20%; [45-89]; mean: 68 y) and female ($n = 15$; 65.22%). The average age of their current dentures was 1.57 years, with a range between one ($n = 10$; 43.5%) and two years ($n = 13$; 56.5%). Regarding the frequency of denture's hygiene, although the clear majority of individuals did clean their denture at least twice a day ($n = 15$; 65.2%), 30.4% ($n = 7$) did it only once a day, and 4.3% ($n = 1$) did not clean. The 69.6% ($n = 16$) of the sample reported having already used denture adhesives before, however, 62.5% ($n = 10$) had stopped using them, reported the bad taste ($n = 2$; 8.7%), and ineffectiveness ($n = 4$; 17.4%) as main causes. The participant-centered outcomes, according to the questionnaire responses, reported that the experimental denture adhesive had longer effectiveness, which for 73.91% ($n = 17$) of the sample was more than 8 hours ($p = .0001$). The control adhesive presented better results, improving the speaking ($p = .003$) chewing ability ($p = .001$) and making the removal/cleaning of the denture adhesive easier ($p = .003$), with statistically significant differences.

Comparing the experimental adhesive with the placebo, the first showed statistically significant better results concerning improved speaking ($p = .004$), better chewing ($p = .001$), degree of satisfaction ($p = .09$) and effectiveness time ($p = .0001$). The control denture adhesive also presented better results than the placebo in the improvement of speech ability ($p = .004$) and chewing ($p = .001$), opinion on utility ($p = .010$), degree of satisfaction ($p = .024$), taste ($p = .009$) and effectiveness time ($p = .0001$). There were no statistically significant differences between the three products in the subjective evaluation of the dentures' retention and stability. The overall intra-observer measurement error was 0.15 gnathometer units, while the overall interobserver measurement error was 0.12 gnathometer units. The intra-observer reliability coefficient was 0.90, while the overall interobserver reliability coefficient was 0.60 g for the dynamometer and 0.80 g for the gnathometer. The ANOVA showed no systematic observer effect in the evaluations with the dynamometer ($p = .178$) and with the gnathometer ($p = .78$).

As shown in Figure 1, no adhesive was used and the mean force needed to dislodge the dentures, measured with dynamometer, was 123.8 ± 38.3 g. When the experimental denture adhesive was used, that necessary force was about 155.8 ± 51.5 g, and with the control denture adhesive was 152.7 ± 52.6 g. Comparisons between products showed statistically significant differences between the initial measurements (without denture adhesive) and the measurements with both the denture adhesives, experimental ($p = .034$) and control ($p = .041$). Also, the differences between the measurements with the placebo and the measurements with denture adhesives, either experimental and control, were statistically significant ($p = .047$ and $.048$, respectively). Although the force required to dislodge the denture with the experimental adhesive was greater than that required with the control denture adhesive, that difference was not statistically significant ($p > .05$).

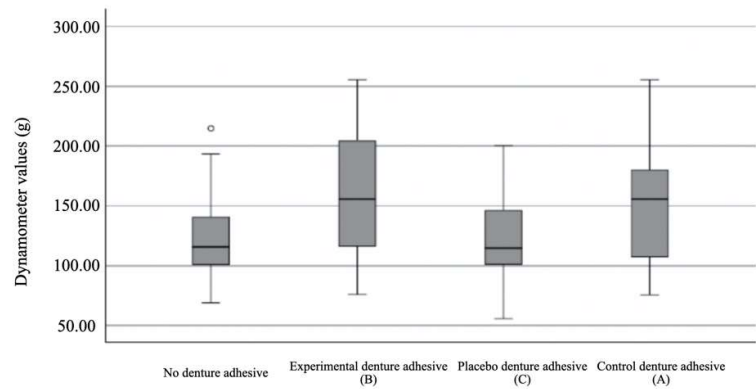


Figure 1. Dynamometer measurements among the different products.

The results of the gnathometer measurements (Figure 2) revealed that, when no denture adhesive was used, the dentures were dislodged with an average occlusal force of 0.8 ± 0.6 units. When the experimental denture adhesive was used, that necessary force was about 1.0 ± 0.6 units, and when the control denture adhesive was used, it was 1.1 ± 0.6 . There were no statistically significant differences between the three groups ($p = .055$).

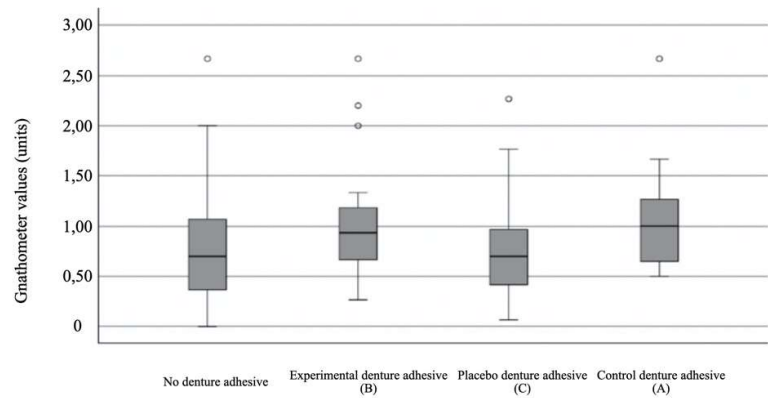


Figure 2. Gnathometer measurements among the different products.

3.2. *In vitro* assessment

The effect of the denture adhesives on SDA, is showed in Figure 3, reported that, after 48 hours, there was no growth of *Candida Albicans* ATCC 11225 in the presence of the denture adhesives, however, after five days, there was growth with both. The experimental adhesive had a higher impact on inhibiting the growth of *C. albicans* ATCC 11225 by showing a significant difference ($p < .05$) in the number of CFUs 5 and 7 days after the test compared to the control adhesive and control (*Candida Albicans* with no product). Although there was a growth of *C. albicans* ATCC 11225 in the presence of the two denture adhesives (experimental and control), the growth was slower and less intense with the experimental denture adhesive.

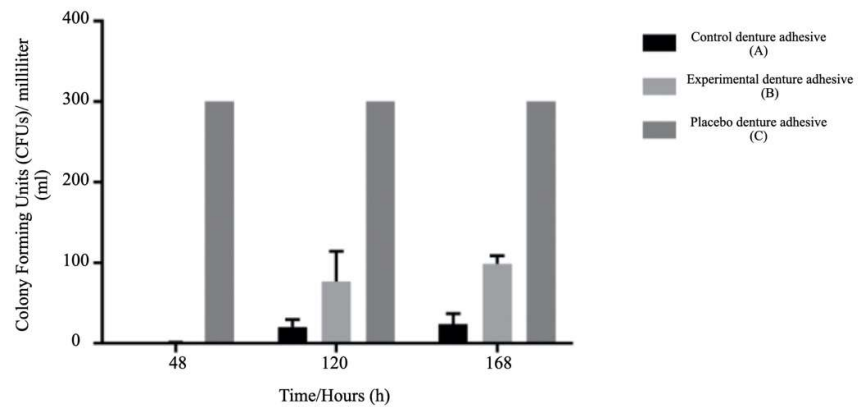


Figure 3. Effect of the denture adhesives on the growth of *C. albicans* ATCC 11225 in SDA medium.

4. Discussion

The null hypothesis was rejected since significant differences were found among the assessed adhesives. The present study selected dentures with a maximum wearing period of two years according to Maeda et al., [21] and a denture needs to be relined after approximately 27 months. The ideal protocol would be the evaluation of new dentures, as in other studies, [10,22] nevertheless, considering the short evaluation period of our study, and the fact that dentures require an adaptation period, a bias could occur. Therefore, we decided that the best method would be to fit and reline the dentures with a hard relining, previously, and then verify that they all had a correct bilateral balanced occlusion. The present study was a phase IV clinical trial, where a new product (OlivaFix® Gold) was evaluated and compared with a product already studied (Kukident Pro®) and a placebo (Vaseline®). Vaseline was selected as the placebo due to its consistency, similar to denture adhesives, and lack of a specific flavor.

This study was designed as a multicenter to evaluate these products more efficiently by obtaining a good sample of participants to satisfy the objective of the study within a reasonable time frame. A previous team meeting was held to standardize the procedures as much as possible, and a pilot study to standardize and calibrate the clinical evaluators. All procedures were recorded in video format in case there were doubts.

Regarding the influence of the products on the improvement of chewing, the control denture adhesive presented better results ($p = .001$) than the experimental denture adhesive, and both these denture adhesives were significantly better than the placebo ($p = .001$ for both). These results agree with several studies [14,23,24] that refer that the use of denture adhesives leads to an increase in the chewing rate and a decrease in the duration of chewing cycles. Although the differences between the two denture adhesives were significant, in descriptive terms, the number of participants who affirmed that their chewing improved with the control denture adhesive was not much higher than those who affirmed it for the experimental denture adhesive ($n = 16$; 69.57% VS. $n = 13$; 56.52%).

Regarding the effectiveness time, the experimental denture adhesive had significantly longer effectiveness than the control ($p < .0001$). These results may be explained by its composition. The experimental adhesive presents an innovative formula using a high concentration of olive oil instead of the ingredients commonly used, such as zinc and petrolatum. Scientific evidence reports that the retention force of a denture adhesive decreases over time, [23] due to its dissolution. [25] As explained above, when the adhesive is in contact with saliva, it absorbs water slowly and increases its volume, thus increasing its viscosity until the hydrophilic polymer particles come into contact with each other, forming a continuous polymer matrix. Subsequently, oral fluids destroy the polymer

matrix, decreasing the viscosity and resulting in a progressively weaker bond strength. Therefore, the olive oil, which is highly viscous, in the composition of the experimental denture adhesive, may explain the significantly longer adhesion effectiveness.

Two quantitative variables were combined in this investigation. First, by using a dynamometer, we tried to simulate the forces made by the participant when speaking, smiling, and doing other daily activities. Then, with the gnathometer, the objective was to simulate movements that occur during chewing. Thus, the combination of these evaluation methods allows us to test a wide variety of movements that can influence the stability of complete dentures. However, it must be highlighted that the evaluated forces do not consider the frequency, duration and magnitude of the functional or parafunctional forces carried out on a daily routine. The average value of the tensile force required to dislocate the denture when using the denture adhesives was approximately 150 g. These results are inferior to those reported in other studies,^{10,26} that ranged from 350 g to 1095 g. However, the study by Pradíes et al., [10] evaluated new dentures, which may justify that observation. Nonetheless, if we analyze the scientific evidence regarding implant-retained overdentures, the retention values found are approximately between 350 and 500N, according to the different retention systems used. [27,28] Thus, the values obtained with denture adhesives would not be expected in the overdentures with ball retention systems, for example.

Finally, regarding the gnathometer values, in general, the results indicated similar mean values for the two denture adhesives. Also, the reported values with the use of denture adhesives were higher than those without these products. However, according to inferential analysis, there were no significant differences between the three products. Other authors obtained average values much higher than ours. [2,11,22] On the other hand, the results obtained by Pradíes et al., [10] with and without denture adhesives, are in agreement with ours. If we do not consider units and focus only on the percentage of increase or improvement with the use of denture adhesives comparing to not using any (37.5%), our study also agrees with that of Polyzois et al. [11] (32.5%) on the evaluation of some denture adhesives.

When interpreting these results, it should be bear in mind that most of the studies with which we are comparing ours, except for the study by Pradíes et al., [10] only obtained measurements from the anterior zone. In contrast, in our study, the evaluations were made in three locations (two posterior and one anterior), and the average value was calculated; this may justify the discrepancies obtained.

Regarding the inhibition of *Candida Albicans* growth, although there was a growth of fungi in the presence of the two denture adhesives (experimental and control), the experimental denture adhesive had a greater effect on inhibiting that growth, with statistically significant differences at 5 and 7 days of the trial. We could expect better results with the control denture adhesive because it has zinc, which is known to have antifungal activity. [29] However, the experimental denture adhesive, which has no zinc in its composition, exhibited a greater antifungal effect. This effect may be due to the organic olive oil in the experimental denture adhesive, which is known to have phenolic components that have anti-inflammatory and even anti-cancer evidence. [30] Dacrory et al. evaluated the use of olive oil by-products in a new antimicrobial hydrogel and discovered that this product has an antimicrobial capacity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida Albicans*. [31] Therefore, although the experimental denture adhesive does not contain zinc (classic antimicrobial) in its composition, the presence of these possible by-products of the organic olive oil may be responsible for the antifungal effect it had in this study.

As a limitation of the laboratory evaluation is that in vitro observations are not always representative of the in vivo situation. The components of saliva and salivary flow, as well as variable intraoral pH, can interfere with the growth of *C. albicans*. Furthermore, since an association between oral streptococci and *Candida Albicans* exists, [32] it would also be important to test the denture adhesives' effect on the growth of oral streptococci.

More multicenter, international studies are needed to assess the differences and similarities between different countries concerning denture adhesives. In addition, educational programs for patients regarding this topic should be created. The reactions and comments of participants can be valuable to the manufacturers of these products, thus improving several less successful aspects. It would also be important to develop guidelines or protocols regarding denture adhesives.

5. Conclusions

Within the limitations previously discussed, the following conclusions can be drawn:

- There were no differences on the force needed to dislodge the denture under traction between the experimental and the control denture adhesives.
- Individuals' evaluation of the dentures' retention and stability was not statistically significant different between the three products.
- The experimental adhesive showed a better effectiveness time than the control and placebo.
- The control denture adhesive improved the ability to speak and chew, taste and odor, and ease of removal, with significant differences.
- The experimental denture adhesive showed the best antimycotic effect against the growth of *Candida Albicans* compared to the control and placebo.

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Institutional Review Board Statement: The protocol was evaluated and approved by the Research Ethics Committee of the Clínico San Carlos Hospital of Madrid, Spain (Trial registration code CEIC 18/515-R_P) following the Declaration of Helsinki of ethical principles for medical research involving human subjects.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

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